

Remarks

Claims 111-113 are pending in the application and stand rejected. These claims have been amended to remove recitation of microRNAs. Claim 113 has been amended to clarify the language of that claim.

No new matter has been added by the present Amendment. Applicant specifically reserves the right to pursue the subject matter of the canceled or amended claims in a related application. The present Amendment is introduced for the *sole* purpose of furthering prosecution. Applicant respectfully requests reexamination and reconsideration of the case in light of the present Amendment and the following Remarks. Each of the rejections levied in the Office Action is addressed individually below.

Rejections under 35 U.S.C. § 112, first paragraph, as allegedly being indefinite

Claims 111-113 stand rejected under 35 U.S.C. § 112, first paragraph, on the ground that recitation of microRNAs in the claims constitutes new matter. Applicant emphatically disagrees with the Examiner's position, but has amended the claims to remove recitation of microRNAs *solely* in order to further prosecution and move the case toward allowance. Applicant, therefore, respectfully submits that the rejection is rendered moot by the present Amendment.

Rejections under 35 U.S.C. § 103(a) as allegedly being obvious

Claims 111-113 stand rejected under 35 U.S.C. § 103(a) on the ground that they are unpatentable over Abe *et al.* (2001, *Eur. J. Pharm. Sci.*, 13:61-69), Tuschl *et al.* (PCT Patent Publication WO 02/44321), Astriab-Fisher *et al.* (2000, *Biochem. Pharmacol.*, 60:83-90), Herweijer *et al.* (US Patent Publication 2002/0165183), as evidenced by Caplen (2003, *Expert Opin. Biol. Ther.*, 3:575-86) and Trubetskoy *et al.* (US Patent Publication 2004/0162235).

The Examiner cites Abe as teaching use of antisense oligonucleotides delivered using liposomes which target the influenza virus nucleoprotein (NP) gene, but acknowledges that Abe does not teach use of an siRNA targeted to the NP gene or use of a cationic peptide as a delivery agent. The Examiner alleges that the other cited references remedy these defects. In particular, the Examiner alleges that Tuschl teaches that siRNA is a more effective and safe alternative to antisense technology, that Caplen teaches that siRNA delivery is associated with the same problems as antisense RNA delivery, that Astriab-Fischer teach inhibition of gene expression

using antisense oligonucleotides conjugated to cationic peptides, and that Herweijer and Trubetskoy teach compositions and/or methods involving siRNA and cationic peptide delivery agents. The Examiner strings together the pieces of these individual teachings to conclude that it would have been obvious to one of ordinary skill in the art to use a cationic peptide for delivery of an influenza siRNA into cells, as recited in the present claims. Applicant respectfully disagrees.

For a § 103 rejection to be proper, the Examiner must establish how and why the cited references render obvious all of the elements of a claim. The Examiner has not met this burden, for example, as Applicant has argued in its previous Office Action Responses. For purposes of efficiency and focused prosecution, Applicant will not repeat its prior arguments here, but maintains those arguments and incorporates them herein by reference. Applicant offers the following new arguments in response to the Examiner's failure to address how the combination of references renders obvious a method involving vascular delivery of an RNAi agent so that the nucleic acid is delivered to the respiratory system, as recited in the claims.

Applicant respectfully submits that no combination of cited references renders obvious the claims, which recite a method involving vascular delivery of an RNAi agent so that the nucleic acid is delivered to the respiratory system. The Examiner states that Abe "teach intravenous delivery of antisense compounds to mouse [*sic*; to a mouse] infected with influenza virus and teach a reduction in the viral target mRNA and a decrease in virus titer in the lungs" (Office Action, page 5). Applicant respectfully submits, however, that one of ordinary skill in the art would not understand the teachings of Abe to be relevant to the claims. Indeed, the antisense compounds described in Abe are *encapsulated in liposomes* for delivery, and the entire reference is focused on the delivery problems that liposomes particularly address. For example, Abe discusses that "liposomally encapsulated" oligonucleotides performed better than non-encapsulated oligonucleotides (Abe, page 67, column 2, lines 11-27), and discusses at length that liposomal encapsulation is particularly useful for addressing problems with "circulation half-life of the oligonucleotides and . . . efficacy," (Abe, page 62, column 1, lines 2-3), "oligonucleotide stability, cellular uptake, subcellular availability, and other pharmacokinetic parameters" (Abe, page 62, column 2, lines 8-13), "macromolecule entry into living cells while avoiding the lysosomal pathway" (Abe, page 65, column 2, lines 11-12). Thus, one of ordinary skill in the art would understand the teachings of Abe to be specific to delivery of nucleic acids via liposomal

encapsulation, and that Abe, in fact, *teaches away* from methods involving *non-encapsulated* nucleic acids.

Applicant respectfully submits that none of the cited references remedies the defects of Abe. Tuschl makes absolutely *no mention* of delivery to the respiratory system, and *certainly* does not mention vascular administration so that the nucleic acid is delivered to the respiratory system, as recited in the claims. In addition, Astriab-Fischer describes *in vitro* cell culture experiments, and makes no mention of vascular administration so that the nucleic acid is delivered to the respiratory system, as recited in the claims.

Although Herweijer mentions injecting nucleic acids to cause an effect in lungs, Applicant respectfully submits that one of ordinary skill in the art would *not* understand it to render obvious the claims. Herweijer describes one experiment in which a DNA plasmid encoding a reporter gene was complexed with polyethyleneimine and polyacrylamide and injected into mice, and expression of the reporter gene was observed in the lungs (Herweijer, Example 5). Applicant respectfully submits that Herweijer is not relevant to methods involving vascular administration so that the nucleic acid is delivered to the respiratory system, as recited in the claims. Indeed, Example 5 of Herweijer relates to delivery of *plasmid DNA* using *synthetic polymer delivery agents* in order to *promote gene expression*. As discussed in Applicant's previous Responses, (1) DNA plasmids are *large DNA molecules*, which have different chemical properties and behaviors than do small RNA molecules; and (2) *synthetic polymer* delivery agents have different chemical properties and behaviors than do cationic peptides. Moreover, the teachings of Herweijer relate to methods of *promoting* gene expression, not inhibiting it. For all of these reasons, one of ordinary skill in the art would not consider the teachings of Herweijer to be *at all* relevant to cationic peptides for delivery of siRNAs or shRNAs, as recited in the claims.

Finally, as acknowledged by the Examiner, Caplen was published *after* the priority date of the present application and is, therefore, not available as art against the present case. Even if Caplen *were* available as art against the present case, it would *not* render obvious the claims. Caplen makes a conclusory statement that siRNAs injected into mice can be taken up by lungs, but does not describe use of cationic peptides as delivery agents. Indeed, Caplen makes no mention of cationic peptides *at all*. The teachings of Caplen, therefore, suffer defects similar to those of Abe and *certainly* do not remedy the defects of Abe. Thus, (1) Caplen is *not available*

as art against the present application, and (2) *even if it were*, one of ordinary skill in the art would not understand it to render obvious the present claims.

Similarly, Trubetskoy was also filed *after* the priority date of the present application and is, therefore, not available as art against the present case. Applicant, therefore, respectfully submits that these references were improperly included in the § 103 rejection and cannot serve as a basis for rejection. Even if Trubetskoy *were* available as art against the present application, it would *not* render obvious the claims. Trubetskoy describes one experiment in which an siRNA was complexed with a polyethyleneimine-poly aspartic acid ampholyte was injected into a mouse tail vein and an effect was observed in the lung (Trubetskoy, Example 7). Applicant respectfully submits that these teachings are not relevant to methods involving vascular administration so that the nucleic acid is delivered to the respiratory system, as recited in the claims. Indeed, Example 7 of Trubetskoy relates to delivery of an siRNA using a *synthetic polymer* complexed with an *anionic* peptide. As previously discussed, (1) a synthetic polymer has different chemical properties and behaviors than does a cationic peptide; moreover, (2) an *anionic* peptide also has different chemical properties and behaviors than does a cationic peptide. Thus, one of ordinary skill in the art would not consider the teachings of Trubetskoy to be *at all* relevant to cationic peptides for delivery of siRNAs or shRNAs, as recited in the claims.

Moreover, Trubetskoy *teaches away* from compositions that comprise a delivery agent *consisting essentially of* at least one cationic peptide, as recited in the claims. In particular, Trubetskoy teaches an siRNA delivery agent that is a polyampholyte, an entity that contains “*both polycations and polyanions in the same polymer*” (Trubetskoy, paragraph 25; emphasis added). In contrast, the present claims recite compositions that comprise an RNAi agent and a delivery agent *consisting essentially of* at least one cationic peptide.

Indeed, the entire disclosure of Trubetskoy relates to ampholytes, and that it is, in fact, *crucial* to include *both* the polyanion compound *and* the polycation in order to effectively deliver siRNAs. For example, Trubetskoy states that “the presence of an excess of polycations may be toxic to cells or may adversely affect biodistribution of the complexes *in vivo*” (Trubetskoy, paragraph 10). Trubetskoy further explains that “addition of polyanions to the point of near charge reversal of the complex dramatically increases the efficacy of gene transfer mediated by DNA/polycation complexes” (Trubetskoy, paragraph 23). Thus, Trubetskoy teaches that the *combination* of polyanion + polycation is *crucial* for efficient delivery of siRNA. In contrast, the

present claims recite compositions comprising an RNAi agent and a delivery agent consisting essentially of at least one cationic peptide. Thus, (1) Trubetskoy is *not available as art* against the present application, and (2) *even if it were*, one of ordinary skill in the art would not understand it to render obvious the present claims and (3) would, instead, understand it to *teach away* from the claims.

Applicant, therefore, respectfully submits that no combination of the cited references would lead one of ordinary skill in the art to the present claims. Indeed, one of ordinary skill in the art would have no reasonable expectation of success in using *cationic peptides* for delivery of *short RNA molecules*. Moreover, Abe actually *teaches away* from the present claims. Applicant, therefore, respectfully submits that the claims are not obvious over the cited references, and respectfully requests that the rejection be removed.

Obviousness-Type Double Patenting

The Examiner has levied a *provisional* obviousness-type double patenting rejection, asserting that claims 111-113 pending in the present application are not patentably distinct from claims 12, 22, and 24-27 of co-pending U.S. application U.S.S.N. 11/259,434. Applicant respectfully refrains from commenting on this rejection until such time as it matures into an *actual* rejection.

Conclusion

For all of the reasons set forth above, each of the rejections in this case should be removed and the application should proceed to allowance. A Notice to that effect is requested.

If, at any time, it appears that a phone discussion would be helpful, the undersigned would greatly appreciate the opportunity to discuss such issues at the Examiner's convenience.

Respectfully submitted,

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